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GENERAL PRACTICE

TOXIC REACTIONS TO LOCAL ANÆSTHETIC DRUGS

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MANY PHYSICIANS are not familiar with the hazards of local anæsthesia and have insufficient knowledge of the pharmacology, maximum dose recommended, and the systemic effects of these drugs. This statement applies especially to Pontocaine hydrochloride (known officially as tetracaine in the U.S.A. and amethocaine in the U.K.), used as a surface anæsthetic agent.

The toxic effects of procaine, cocaine and other local anæsthetic agents have been known for many years and the pioneers soon realized that rapid absorption of these drugs into the circulation could result in reaction.

INCIDENCE OF DEATHS

Accurate figures on the frequency of fatal reaction are not available, because many cases are not reported as such.

In 1924 and again in 1928 the American Medical Association set up a commission to study fatalities from local anæsthetic drugs in use at that time. They reported on 43 deaths in 1924 and 14 in 1928; in nearly all cases procaine and cocaine were the drugs used. Though, as a result of this survey, recommendations for safe dosage and technique were made, many deaths continue to be attributed to these and similar drugs. Since 1933, tetracaine has been added to this list.

Criep and Ribeiro[1] in 1953 reported three cases of fatal allergic reaction to procaine hydrochloride.

Adriani[2] found 10 unreported deaths from topical tetracaine used for endoscopic procedures performed over a 15-year period at Charity Hospital, New Orleans, and five others from hospitals in the same geographical area.

Richards[3] reported two deaths following application of 2% amethocaine (tetracaine) hydrochloride spray. Both anæsthetics were to permit bronchoscopy, and in both cases generalized convulsions set in within a few minutes and death followed shortly afterwards. The amount of agent used in each case was not known. The same author reported another case of a man who had a deflected septum treated by local application of an adrenaline swab dipped in cocaine crystals; he died in convulsions within a few minutes.

Jackson[4] reviewed the literature for cases of local anæsthetic reaction occurring in the U.K. Twelve fatalities from amethocaine used topically for endoscopic work were reported by various authors. Many of the deaths occurred in chronically ill or cachectic patients, two in chronic asthmatics. Jackson stated that overdosage and faulty technique were responsible for the fatal reactions.

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PHARMACOLOGY

Most of these agents in common use are nitrogenous compounds. Tetracaine and procaine are esters of para-aminobenzoic acid. Cocaine is an ester of benzoic acid. Lidocaine is not an ester but has the same chemical configuration as procaine.

These drugs all stimulate the cerebrospinal axis from above downward. After intravenous injection, the sensory areas of the cortex are stimulated, resulting in increased mental keenness and excitement. Motor activity is increased as indicated by restlessness, tremors, convulsions progressing to paralysis and coma depending on the blood level. The agents are all hydrolyzed by the liver.

FACTORS INFLUENCING GENERAL TOXICITY

Systemic toxicity of a drug depends on the amount in the circulation at any one time. This depends on the following factors:

Amount of Drug Administered, Potency and Concentration.

There is a great variation of toxicity from one agent to another. From animal experiments the following figures have been derived. If for comparison we allot to procaine the arbitrary standard of 1, that for Metycaine (piperocaine) would be 3; for cocaine 4; tetracaine 12 to 20; and nupercaine (dibucaine) 20.[6]

Though these figures are not strictly applicable to man, there is for the average healthy individual an average dose by weight for each agent. This figure will vary according to patient's age, size, state of nutrition and metabolism associated with any existing debilitating disease.

Also important is the fact that toxicity of a drug increases in geometrical and not arithmetical progression with increase in concentration. Thus a given quantity of a 2% solution has 16 times the toxicity of a similar quantity of 0.5% solution. The rule follows that one should use the lowest concentration adequate for satisfactory anæsthesia.

Rate of Absorption from Site of Injection.

The greater the vascularity of the tissues injected, the more rapid is the absorption. Areas of increased vascularity include mucous membrane surfaces of the respiratory tract, stomach and urethra, the scalp, face, neck, caudal canal, perineum and corpus cavernosum. All agents except cocaine are powerful vasodilators when used topically and without vasoconstrictors.

Regarding absorption of an agent from mucous membrane surfaces, Adriani[2] has shown experimentally that a designated quantity of a drug that results in no detectable blood level when injected subcutaneously gives levels when applied topically that are equal to 1/3 to 1/2 of that after intravenous injection.

Rate of Destruction and Elimination.

The more rapidly or easily a drug is detoxified, the less systemic toxicity it manifests. In a healthy person, detoxification is rapid, while in debilitated, cachetic patients with low basal metabolic rate (B.M.R.), elimination is delayed.

Inadvertent Intravascular Injection.

This is an accident which can be avoided by repeated preliminary aspiration tests.

Water Solubility and its Ability to Diffuse Through Mucous Membranes.

These are important characteristics of any drugs used in topical anæsthesia. For example, benzocaine is poorly soluble in water, being absorbed more slowly than cocaine or tetracaine, and reactions are practically unknown. For this reason it is popular and safe as a lubricating anæsthetic jelly among anæsthetists and urologists.

Susceptibility of Patient.

The terms "idiosyncrasy" and "hypersensitivity" are generally applied loosely. Only after errors in dosage, concentration and techniques are ruled out can one consider the above as a cause of reaction. There are no adequate tests to identify potential reactors but a previous history of a reaction should be sufficient warning.[6]

SYSTEMIC EFFECTS

It has been mentioned that these drugs stimulate the central nervous system. The other most important effect is depression of the myocardium with resultant changes in excitability, conduction and force of contraction.

Intravenous injection of procaine in animals produces characteristic electrocardiographic changes. There is heightening of the T wave, reduction in QRS amplitude, depression of S-T segment, prolongation of P-R interval, and increased width of QRS complex. Continued injection will eventually cause ventricular fibrillation.[7] This depressant effect of local anæsthetic drugs has been utilized to decrease cardiac irritability during thoracic surgery.

ALLERGIC REACTION

This type of reaction manifests itself as skin eruptions such as urticaria, contact dermatitis or angioneurotic œdema. Contact dermatitis can occur from application of anæsthetic ointments and has occurred in dentists who handle local anæsthetic drugs.

A rare histamine-like reaction, found in about 1% of severe cases, is characterized by signs of hypersecretion of lungs and bronchospasm. The three cases reported by Criep and Ribeiro[1] illustrate this type of fatal reaction. They recommend preliminary testing with local anæsthetic drugs in cases of suspected allergy, to determine whether it is safe to continue with the drug. Treatment of an allergic reaction includes administration of oxygen, sympathomimetic drugs, antihistamines and corticosteroids.

SIGNS AND SYMPTOMS

Adriani[8] recognizes two main types of toxic reaction: (1) the circulatory or depressant type; (2) the stimulating or convulsive type.

In (1) the onset is usually abrupt with pallor, feeble pulse, fall in blood pressure, syncope, increasing collapse progressing to cardiac arrest. These signs may follow the injection of a minute amount of the drug. A milder reaction with slower appearance of symptoms may occur and the patient's condition may not progress to collapse. The latter type can be controlled by administration of an analeptic and oxygen, with the patient in the Trendelenburg position. When complete collapse with cardiac arrest occurs, immediate cardiac massage and ventilation with 100% oxygen should be started. This form of reaction fortunately is less common than the stimulating variety.

(2) The stimulating or convulsive type may have an abrupt or delayed onset, may be mild or severe, and can also occur after use of a small amount of agent.

Early symptoms are nervousness, apprehension, headache, slurred speech, dizziness, blurred vision, roaring in the ears, sighing respiration, yawning, dyspnœa, tremor, twitching, and nausea or vomiting. The reaction may stop here or may progress to convulsions, paralysis and unconsciousness.

Pulse and blood pressure may be unchanged at first or there may be tachycardia with a rise in blood pressure. There may then occur a rapid fall in blood pressure with bradycardia and cyanosis. In a severe reaction due to rapid absorption of a large dose of the drug, the patient may pass rapidly from the early to the convulsive phase, and then to paralysis, coma and circulatory collapse.

The early use of intravenous barbiturates with ultra-short action will control the signs of cerebral stimulation. A sufficient amount should be injected in 25 to 50 mg. doses until convulsions are controlled, remembering that a period of 3 or 4 minutes precedes the peak of action.

Symptoms due to the vasoconstrictor agent mixed with the local anæsthetic drug may occur and may be difficult to differentiate from a true reaction. A toxic reaction from epinephrine manifests itself as nervousness, tremors, anxiety, palpitations, precordial distress, tachycardia, and rise in blood pressure and respiratory rate. Bradycardia, however, usually indicates a true local anæsthetic reaction.

TETRACAINE (PONTOCAINE) REACTIONS

Toxic effects from the use of this drug as a topical agent are common. Adriani[2] considers its potency and toxicity to be 10 times that of procaine. Thus, since for the average healthy adult the maximum injectable dose of procaine is 1 g. (1000 mg.) it follows that 100 mg. tetracaine (i.e., 5 c.c. of 2% solution) should be the maximum dose for infiltration. Since absorption from mucous membranes is so rapid, this dose should be considerably reduced for topical anæsthesia.

Consistent findings in Adriani's fatal cases include overdosage, faulty technique, lack of preparation and delay in resuscitative measures. Most cases were characterized by the abrupt, rapidly progressive collapse type of reaction without convulsions. At the Charity Hospital, New Orleans, tetracaine has been discarded in favour of cocaine as the topical agent of choice. The number of reactions reported is much smaller, and they are of the stimulating, convulsive variety.

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Ireland[9] and co-workers conducted a survey of the larger otolaryngology clinics in the United States and Canada to compare the relative toxicity and potency of cocaine and tetracaine. Their findings can be summarized as follows: (1) The number of deaths from cocaine used in 31,885 cases was 3; the number of deaths from tetracaine used in 7394 cases was 4. (2) Concentration of drugs used: (a) cocaine—10% in nose and pharynx, 5% in larynx and trachea; (b) tetracaine—2% in nose and pharynx, 1% in larynx and trachea. Most clinics recommend limiting the intratracheal dose of tetracaine to 2 c.c. of 1% solution. (3) By guinea-pig experiment the mean fatal dose was determined for cocaine as 24 mg./kg. and tetracaine 7.2 mg./kg., giving a relative toxicity of tetracaine/cocaine of 3½/1. (4) Though tetracaine was generally used in 1/5 the concentration of cocaine, it was thought that tetracaine would be the safer drug but the survey did not bear this out. (5) Cocaine is by far the more popular of the two.

There are still many, however, who feel that tetracaine is too valuable a drug to be discarded. One of its best supporters is Carabelli,[10] who reports a series of 621 bronchoscopies in adults using a 0.25% solution, in a one-hand micro-atomizer and a mirror cannula permitting use of small doses of tetracaine. He used an average dose of 14.75 mg. tetracaine (0.737 c.c. of a 2% solution) with no complications. Premedication consisted of morphine or atropine but no barbiturate. In no case was a barbiturate required to counteract a reaction. In reviewing the literature, he found that all authors reporting the actual quantity of the drug used had far exceeded the dose recommended by the manufacturers. One operator was using 15 times the recommended dose for his bronchoscopies. Carabelli[10] suggests a maximum dose of 20 mg. applied in fractional doses in topical anæsthesia. Weisel and Tella[11] reported 1000 bronchoscopies using 2% solution in doses not exceeding 40 mg. They had 19 reactions—12 mild and seven severe—with no fatalities. Six of the latter were of the convulsive variety. One patient had pronounced bronchospasm and status asthmaticus. They feel that reactions can be prevented and controlled by barbiturates and that heavy premedication is indicated.

Reactions from tetracaine used in spinal or regional anæsthesia are practically non-existent. Adriani[2] reports that at the Charity Hospital, New Orleans, spinal anæsthesia was induced with tetracaine 20,000 times, with no untoward reaction. Moore[12] reported using tetracaine for regional anæsthesia in 1004 cases with one reaction and no fatality. He used the solution in concentrations varying from 0.1% to 0.5%, 0.15% being the most popular, and the total dosage of 1 mg. per lb. weight was seldom exceeded. Vasopressor drugs included in solution were epinephrine and Neosynephrin (phenylephrine). Although the injectable dose often exceeded that recommended by the manufacturer, the dilute concentration of tetracaine solution used combined with the vasoconstrictor action was responsible for freedom from reaction. In spinal anæsthesia the low dosage (maximum dose 20 mg.) and slow absorption from the spinal canal explain the absence of toxic reaction to tetracaine.

PREVENTION OF REACTIONS IN TOPICAL AND REGIONAL ANÆSTHESIA

Any patient with a history of allergy or asthma should be protected with barbiturates, antihistamines and bronchodilators.

A previous local anæsthetic reaction should be a warning to give a general anæsthetic unless there are strong indications for use of local. A previous reaction should be investigated, and if the drug is known an agent from a different chemical group should be used.

Premedication should include a short-acting barbiturate since it has been shown experimentally that it protects animals from the stimulating effect of local anæsthetic drugs. Morphine relieves pain and apprehension but should be avoided in asthmatics. The belladonna drugs, atropine or hyoscine, should be given in case a general anæsthetic is required. Food should be withheld prior to any procedures.

Avoid topical anæsthesia in inflamed or traumatized mucous membranes.

Caution the patient not to swallow the agent because of danger of rapid absorption from stomach mucous membranes.

Avoid intravascular injection by repeated aspiration tests when injecting gums, nose, pharynx, larynx, trachea, scalp, face, neck, corpus cavernosum and caudal canal. Avoid rapid injection.

Use vasoconstrictor solution with local where possible, as this delays absorption into the general circulation and does not alter the anæsthetic effect.

Use the most dilute solution adequate for anæsthesia and the minimal dose required.

Maintain continuous contact with the patient at all times. Beware of a talkative, excited patient who suddenly becomes quiet and still. A patient may pass from a stage of overstimulation rapidly to unconsciousness and depression.

Be prepared for any reaction by having immediately at hand equipment and drugs for resuscitation and a plan for action in case of cardiac arrest.

TREATMENT

If the signs of a severe reaction are at hand, place the patient in slight Trendelenburg position and administer 100% oxygen. An emergency resuscitation set with bag and mask is required for assisting depressed respirations and taking over in apnœa.

While the above is being attended to, an intravenous should be started to provide an avenue for subsequent intravenous administrations.

For hypotension give Neosynephrine in 0.2 to 0.5 mg. intravenous doses; better still, by mixing 2 c.c. of 1% solution (20 mg.) with 1000 c.c. of 5% dextrose and water, one can alter the rate of flow according to the blood pressure. Vasoxyl is another valuable vasoconstrictor which can be used in doses of 10 mg. It has minimal central nervous system side-effects.

For severe apprehension, excitement, restlessness or convulsions, give intravenously a short-acting barbiturate such as Nembutal sodium (pentobarbitone) or sodium Pentothal (thiopentone) in doses of 25 to 50 mg.

A good airway is required and endotracheal equipment should be at hand. If cardiac arrest is suspected, immediate cardiac massage is indicated.

SUMMARY

Many physicians are unaware of the hazards of local anæsthetic agents and are unprepared to cope with severe reactions.

Most local anæsthetic agents are nitrogenous compounds and all stimulate the cerebrospinal axis and depress the myocardium. Though many deaths have been reported from topical application of tetracaine, it is generally agreed that this valuable but potent agent has frequently been used in excessive amounts and without consideration of rapidity of absorption from mucous membrane surfaces.

Factors influencing general toxicity, signs and symptoms are discussed and measures for prevention of reaction and treatment are outlined.

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MEDICAL ECONOMICS

COMPREHENSIVE INSURANCE FOR PHYSICIANS' SERVICES

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COMPREHENSIVE physicians' services can be provided satisfactorily under a voluntary health insurance plan sponsored by a medical society and run on a fee-for-service basis.

This is the general conclusion derived from an extensive study of one such plan, Windsor Medical Services, Inc., of Windsor, Ontario (Canada). The study was made by the Bureau of Public Health Economics, School of Public Health, University of Michigan, under a grant from Health Information Foundation.

Data covering the experience of 1954 were obtained by interviews during 1955 with an area-probability sample of the Windsor population and with virtually all Windsor physicians. In addition, an audit of the plan's administration was made.

Less than 5% of the American population subscribes to plans that provide comprehensive physicians' benefits. Most of these plans are not sponsored by the organized medical profession, and most of them alter traditional aspects of medical practice. Windsor Medical Services has been operating successfully for 20 years. Like the typical American physicians' service plan, it is sponsored by the medical society, offers free choice of physician to subscriber, makes fee-for-service payments to physicians, and offers group enrolment of subscribers and coverage of their dependents.

Windsor itself is an urban, industrial community with a population in the study year of about 160,000 in its metropolitan area. In its population make-up and ecological and economic characteristics, it resembles the nearby city of Flint, Michigan, and other medium-sized industrial communities in the United States.

The Windsor plan emerged from the experience of the local Essex County Medical Society in operating a medical relief program for the Ontario government in the mid-1930s. Planned in 1936 and formally chartered in 1937, Windsor Medical Services obtained its first group of subscribers in July 1939.

In this initial contract the plan agreed to cover all medical and surgical services, x-ray and special services, consultations, services of anæsthetists and assistants at operations, preventive medical examinations and refractions, and confinements (including prenatal and postnatal care), in the office, home, or hospital. Excluded was care for such conditions as tuberculosis, mental illness, drug addiction, and acute venereal diseases. A waiting period of six months was specified for treatment of any pre-existing condition.

The services in the present group contract are more liberal. Radium and deep x-ray treatment are now mentioned specifically among the services offered, as are preventive inoculations and cystoscopic and bronchoscopic examinations. Exclusions, similarly, are explained more fully. Waiting periods have been specified for confinements (ten months), refractions and preventive medical examinations (twelve months), and for the removal of tonsils and/or adenoids, herniorraphy, and reparative pelvic, vaginal or perineal surgery (six months).

Although income limits had been adopted and modified during the planning period of WMS, the initial contract was offered to groups of ten or more without income restriction or additional charges. (Income limits for an individual contract then offered were set at $2000.) In 1948 the plan adopted income limits for group subscribers; physicians were permitted to make extra charges to single subscribers earning over $3000 and married subscribers earning over $6500. The only change in income limits since that time was made in 1952, when the limit for single subscribers was increased to $4000. In actual practice, not many families are affected by these income restrictions.

Since 1939 WMS has revised the premiums for its comprehensive group plan five times. In the original contract the monthly premium was $1.09 for the subscriber and for each dependent. The present monthly premium, adopted in February 1956, is $2.30 for a single subscriber, $4.90 for husband and wife, $6.50 for husband, wife, and child, and $7.90 for husband, wife, and two or more children. (In addition, most